



- *Association of British Clinical Diabetologists*
- *Spring Meeting*
- *Newcastle - Gateshead*
- *May 2010*



Presentation and Referral Pathways for Neuroendocrine Tumours

Dr. Andy James

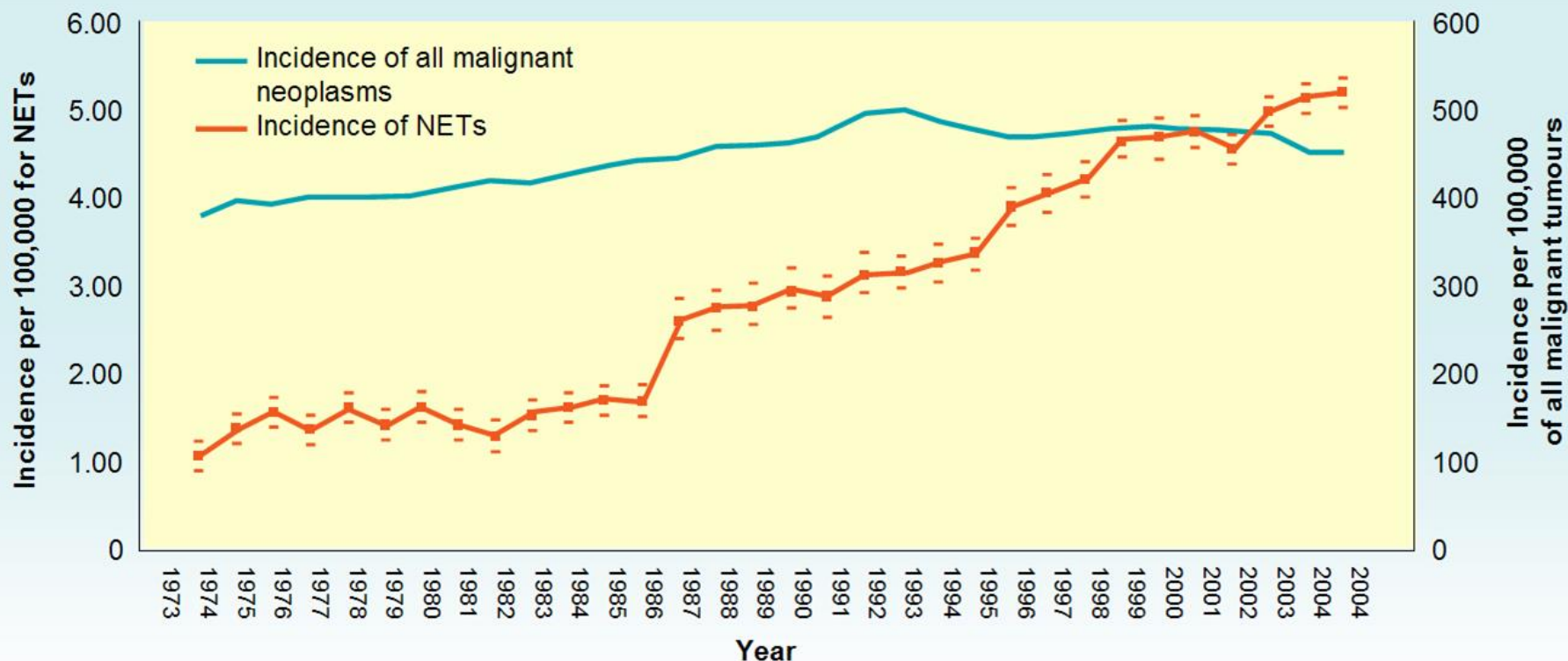
Consultant Endocrinologist

Royal Victoria Infirmary

Incidence of GEP NETs

An observed increase in the incidence of NETS over the last 30 years suggests they are more prevalent than previously reported^{1,2}

Incidence of NETs = 5.25 / 100,000²



1. Modlin IM et al. Cancer 2003; 97: 934–59

2. Yao JC, Hassan M, Phan A, et al. J Clin Oncol. 2008;26(18):3063–72

Risk Factors

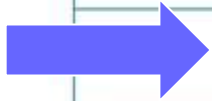
- No risk factors have been proven, but some associations reported:
 - Link between socioeconomic status and incidence¹
 - Suggestions of familial clustering in Swedish Studies¹
 - Smoking suggested to increase risk of small bowel carcinoid tumours²
- Some GEP NETs may increase risk of developing other tumours¹

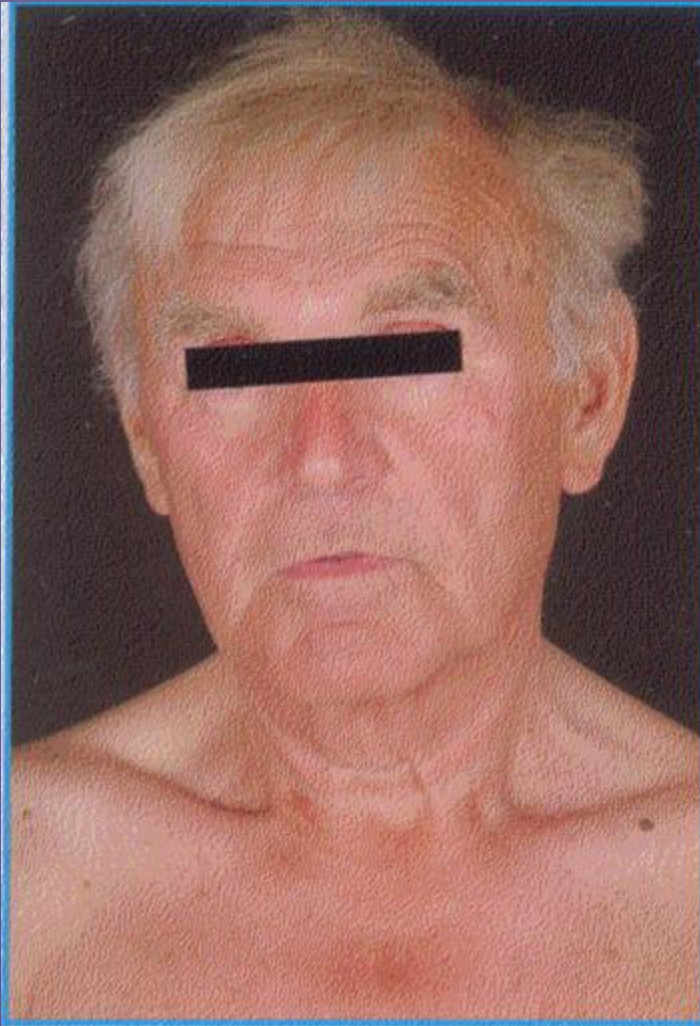
1. Taal BG, Visser O. Neuroendocrinol. 2004;80:3-7

2. Kaerlev L, Teglbjaerg PS, Sabroe S, et al. Cancer Causes Control. 2002;13(1):27-34

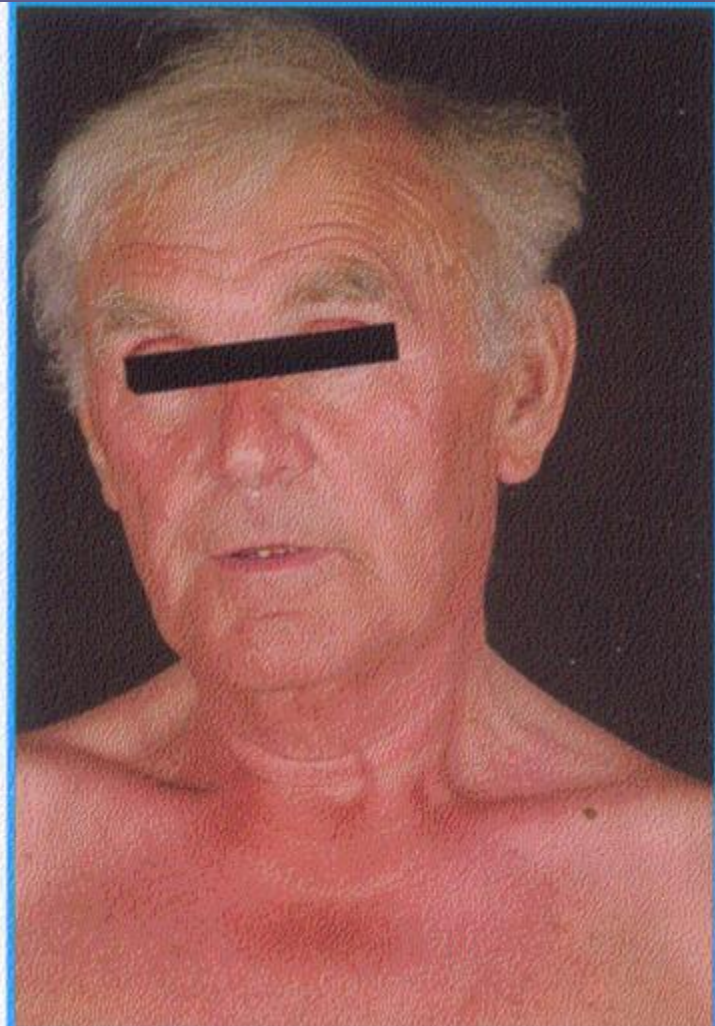
Expected incidence of NETs in the UK (total number per year)

Tumour type	Incidence	Expected number
Non-functioning	20–50 per million	1200–3000
Carcinoid	20 per million	1200
Insulinoma	1–2 per million	60–120
Gastrinoma	1 per million	60
MEN-1	1 per million	60
VIPoma	1 per 5 million	12
Glucagonoma	1 per 5 million	12
Somatostatinoma	1 per 10 million	6





Before flushing



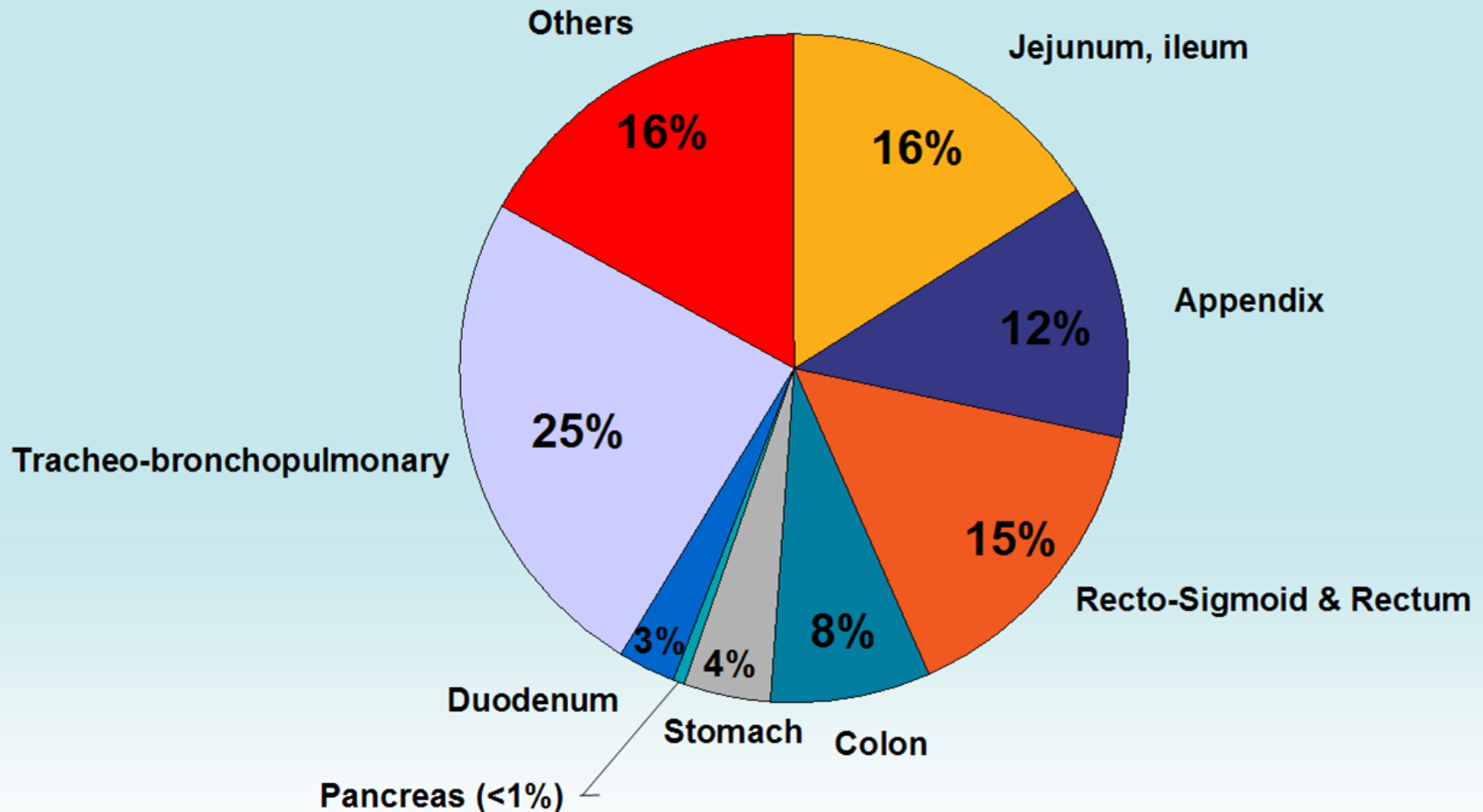
Flushing

Carcinoid Syndrome – Usually reflects Metastatic Disease

Carcinoid Tumours - Classification

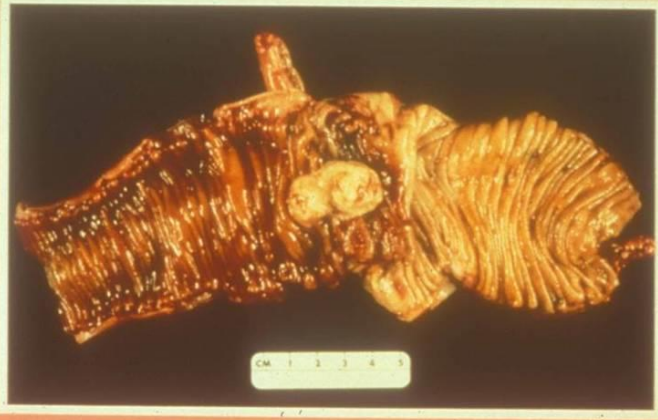
■ Classified according to region of origin

n = 13,715



1. Modlin IM et al. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97: 934-59.

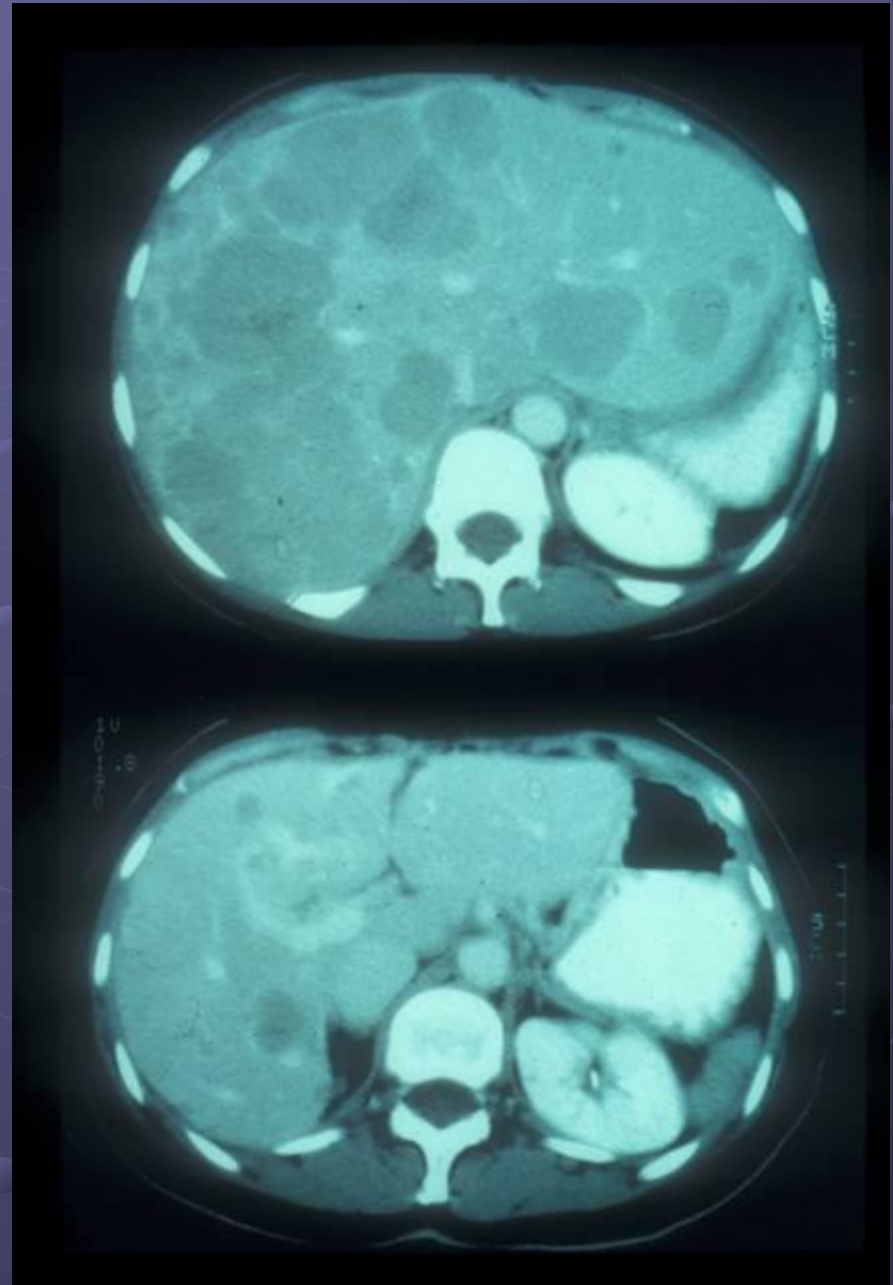
Primary carcinoid tumour of the small intestine



Presentation:

- Incidental finding at surgery
 - Appendectomy
 - Acute/subacute bowel obstruction
 - Anaemia/GI blood loss
- Irritable Bowel Syndrome

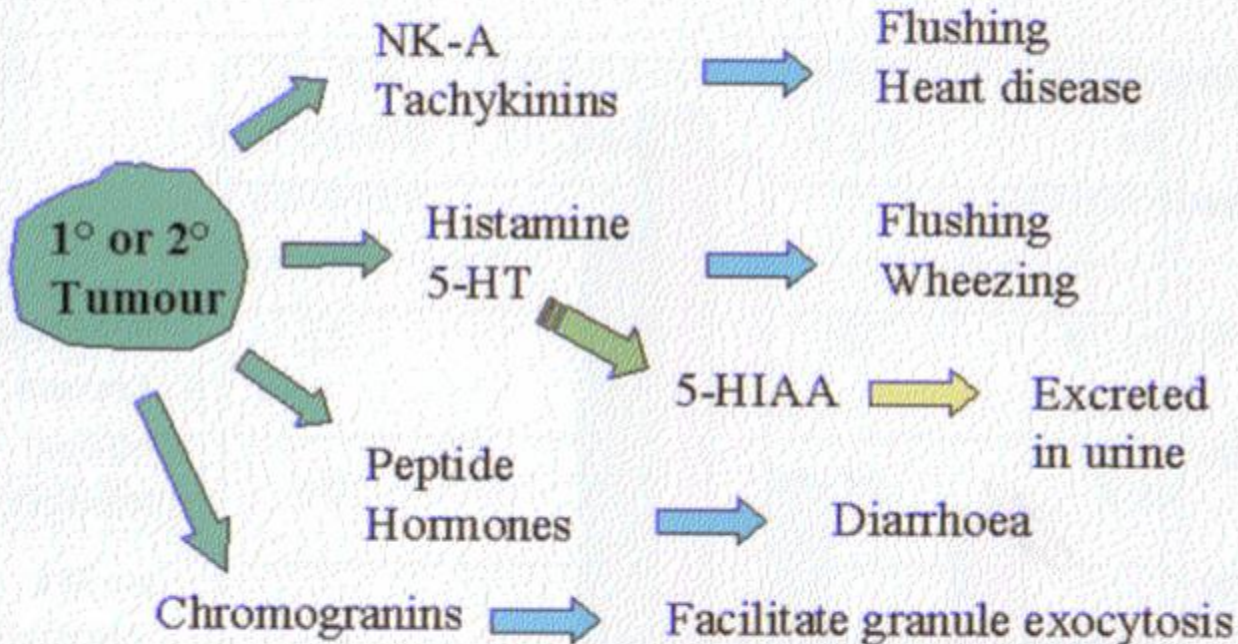
Typical extent of
hepatic metastases in
a patient presenting
with the CARCINOID
SYNDROME
(Flushing/Diarrhoea)





Fibrotic Skin changes with chronic flushing

Mediators Secreted by Carcinoid Tumours and their Effects



NK-A Neurokinin-A
5-HT 5-hydroxytryptamine
5-HIAA 5-hydroxyindole acetic acid

Data from Caplin 1998²³

Carcinoid cardiac disease

- CCD occurs in two thirds of patients with carcinoid syndrome
- One third of patients die from CCD rather than tumour growth
- CCD commonly results in tricuspid regurgitation
- Valve replacement should be considered
- Presence of CCD indicates a poor prognosis



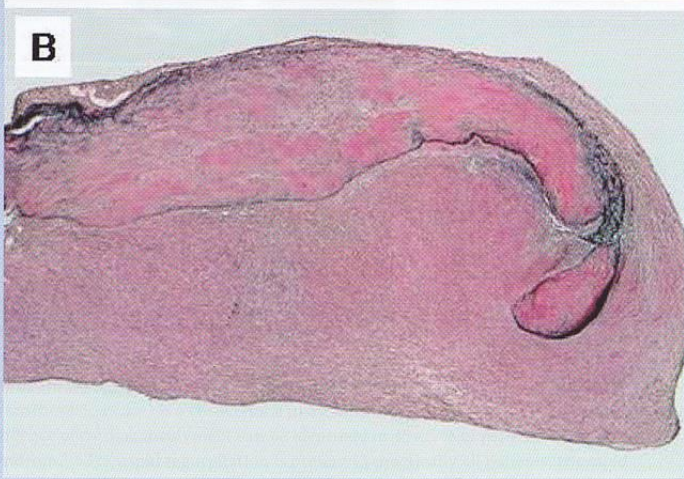
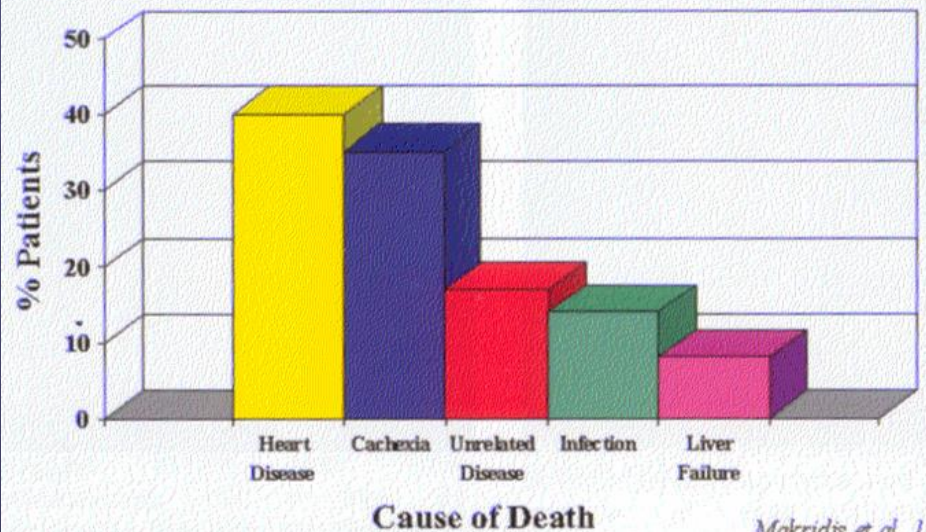


Figure 3. Pathological images of CHD plaques. **3A:** Macroscopic surgical pathologic specimen showing a tricuspid valve with pearly white plaques. **3B:** Microscopic surgical pathologic specimen demonstrating a pulmonary cusp with a "stuck-on" plaque along the arterial aspect. Typical proliferation of myofibroblasts and collagen deposition is seen. (B, Verhoeff-van Gieson). The pictures are kindly provided by Professor W.D. Edwards, the Mayo Clinic, Rochester, USA.

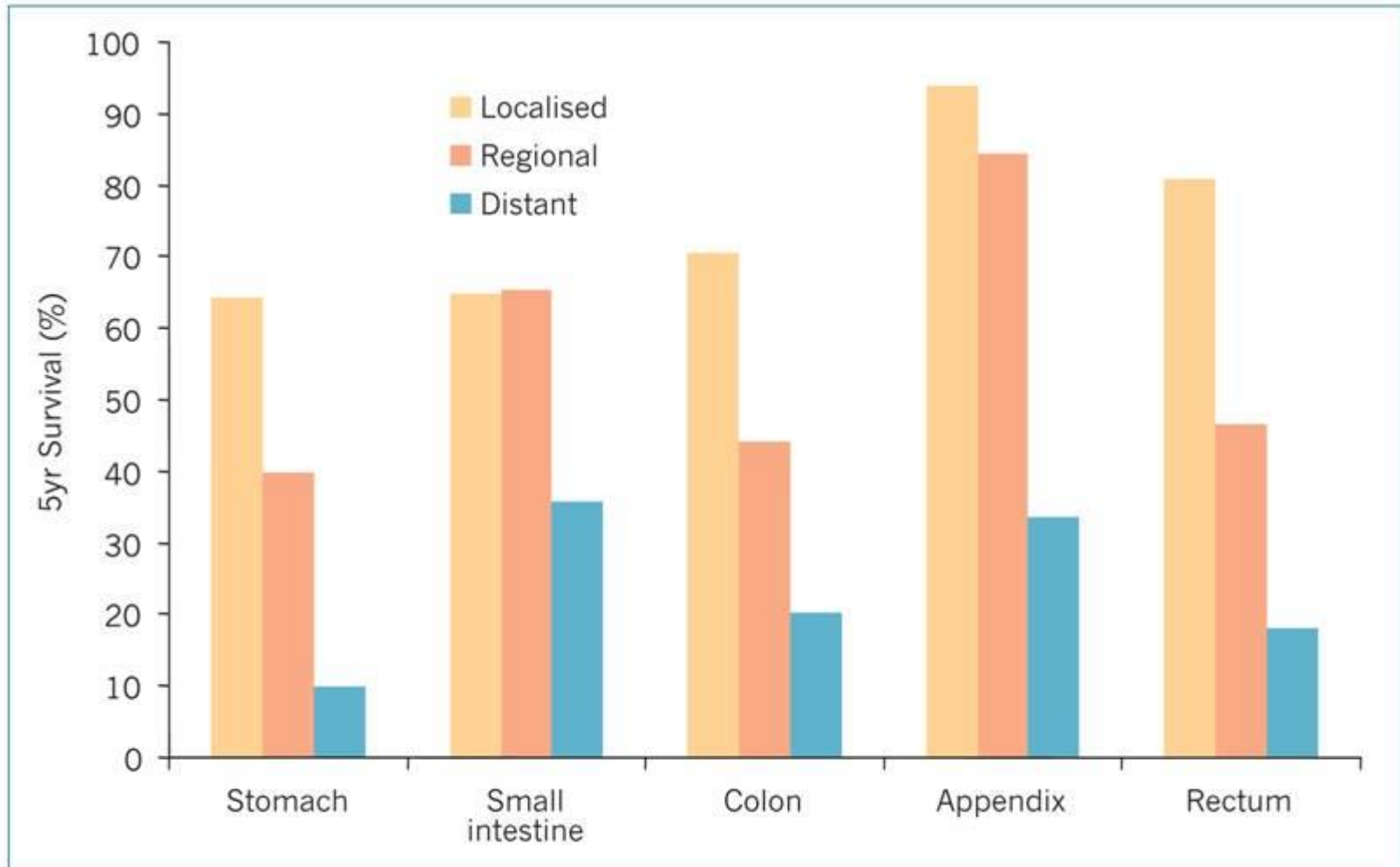
- Carcinoid Valvulopathy
 - Tricuspid regurg
 - Tricuspid stenosis
 - Pulmonary stenosis

Cause of Death In 63 Patients with Advanced Mid-gut Carcinoid Disease



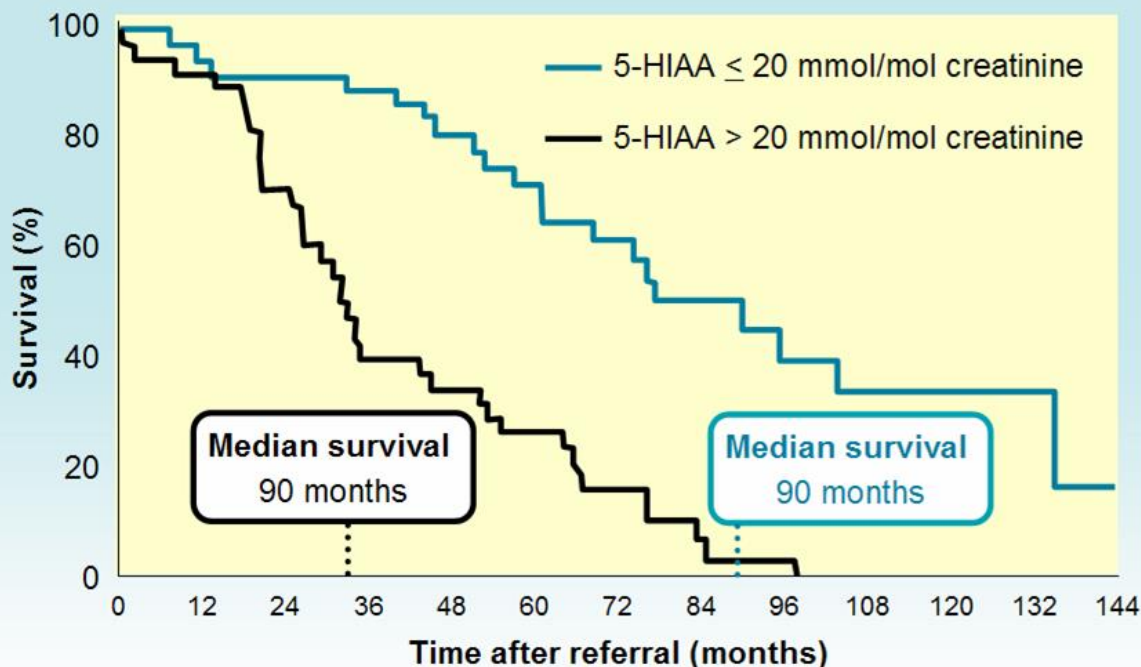
Makridis et al. 1997²¹

5 year survival rates for carcinoids



5-HIAA As An Independent Prognostic Factor

- 5-HIAA can be used to diagnose carcinoid tumours¹
- Unfavourable factors for survival are:²
 - High urinary 5-HIAA levels (>20mmol/mol creatinine)
 - High plasma Chromogranin A (CgA) levels
- 5-HIAA levels > 150mg/day predict a survival of less than 1 year³



- Increased 5-HIAA levels reduce survival by **57 months** ($p= 0.033$)²
- Hazard Ratio of elevated 5-HIAA levels = 3.33^2 (>20 mmol/mol creatinine)

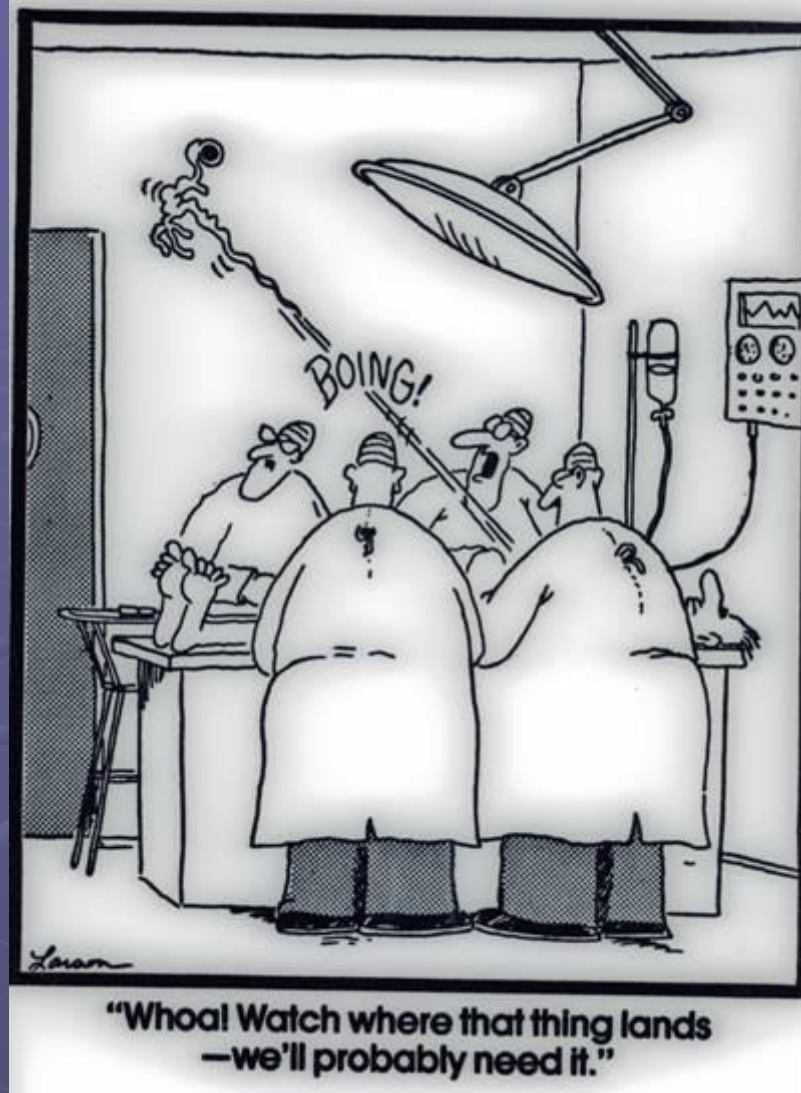
Adapted from Anouk NA et al. Eur J Cancer 2007; 43: 2651-2657

1. Öberg K. Williams Textbook of Endocrinology 2003
2. Anouk NA et al. Eur J Cancer 2007; 43: 2651-2657
3. McCormick D. Gastroenterol Nurs 2002; 25 (3): 105-111

The Newcastle NET Service

- 6 Consultant Surgeons
 - Hepatobiliary/pancreatic
- 2 Endocrinologists
 - Dr. Perros and Dr. James
- 2 Medical Oncologists
 - Dr. Ujjal Mallick
 - Dr. Kate Sumpter
- 1 Interventional radiologist
 - Dr. Rose [FRH]
- PIU support [RVI]
 - Sister's Johnson & Pringle and staff
 - Sister Margaret Miller
 - Sister Margaret Morris
- 1 Dedicated NET Sister
 - Sister Gay Bernstone [FRH]
 - Telephone support ☎
- 2 NET clinic a month
- 1 Nurse lead clinic a week
 - SSA injections
 - Interferon monitoring
 - FGH/tumour markers
- Twice Monthly MDT's
 - The whole team
 - + Dr Sarah Johnson
 - Dedicated Pathology input
 - Ki 67 staining

Newcastle NET service



Dedicated Hepatobiliary Surgeons – Derek Manas, Richard Charnley, Bryan Jacques, Steve White, Jeremy French

The Newcastle NET

Supporting Services

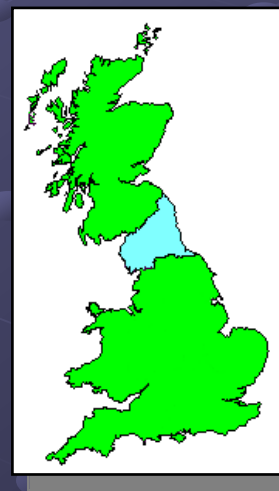
- Medical Physics
 - Octreoscan
 - MIBG scanning
- Biochemistry
 - Hormone assay
 - Belfast bloods
- Upper GI MDT
 - Prof Griffin's team
- NCCT support
 - I131 MIBG ablation
- Dedicated Radiology
 - MRI, CT, U/S,
 - ? PET
 - Particle embolization
 - Radiofrequency ablation
- Royal Marsden Hospital
 - Yttrium octreotate
- Novartis and Ipsen
 - Educational support
 - Nurse Funding
 - NONETS, UKINETS, ENETS support

The Newcastle NET Service 2005

- 165 patients (250)
- 65 on biotherapy (92)
 - somatostatin analogues
 - 4 also on interferon
- 2-5 new patient referrals per month

● Demographics

- North East England
- North Yorkshire
- Scottish borders
- Cumberland



The Newcastle NET Service

- Multimodal/individualised patient approach
 - Somatostatin analogue
 - Symptom control
 - Cytostasis
 - Augmentation with Interferon alpha
 - Sequential hepatic arterial embolization
 - Surgical removal
 - Primary lesion
 - Disease debulking
 - 'Shelling out' of hepatic mets
 - Systemic chemotherapy in selected cases
 - Radioligand treatment
 - Yttrium labelled SSA
 - I131 MIBG NCCT

Evolution of analogues and delivery systems

A CHOICE OF SOMATOSTATIN ANALOGUES - monthly depot Rx



**20mg LAR -
£10,800/annum**

Sandostatin LAR - Novartis

(10mg, 20mg, 30mg)



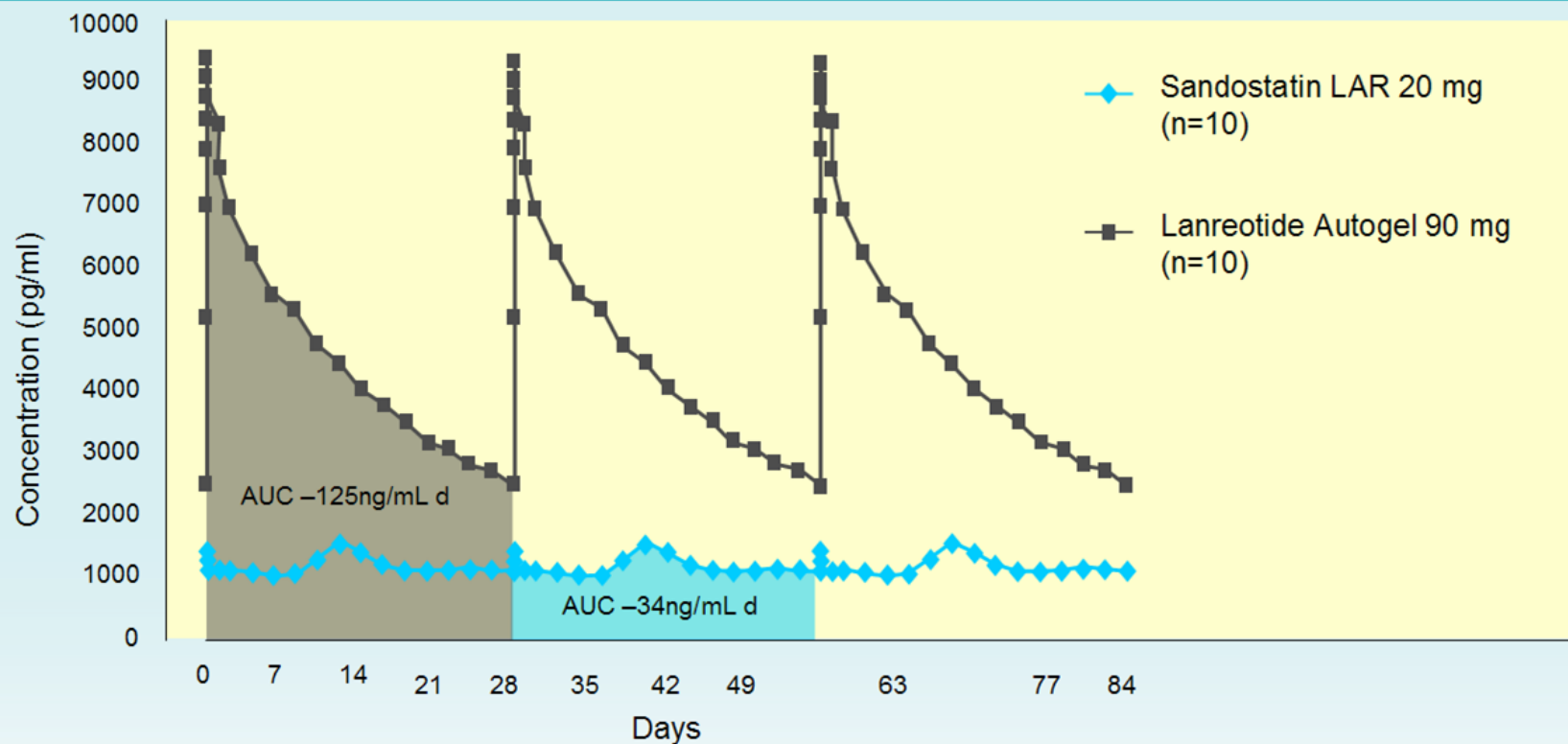
**90mg Autogel -
£9,800/annum**

Lanreotide Autogel - IPSEN

(60mg, 90mg, 120mg)

Pharmacokinetics of Sandostatin® LAR®

Pharmacokinetic profile¹



Target Exposure: 1000pg/ml

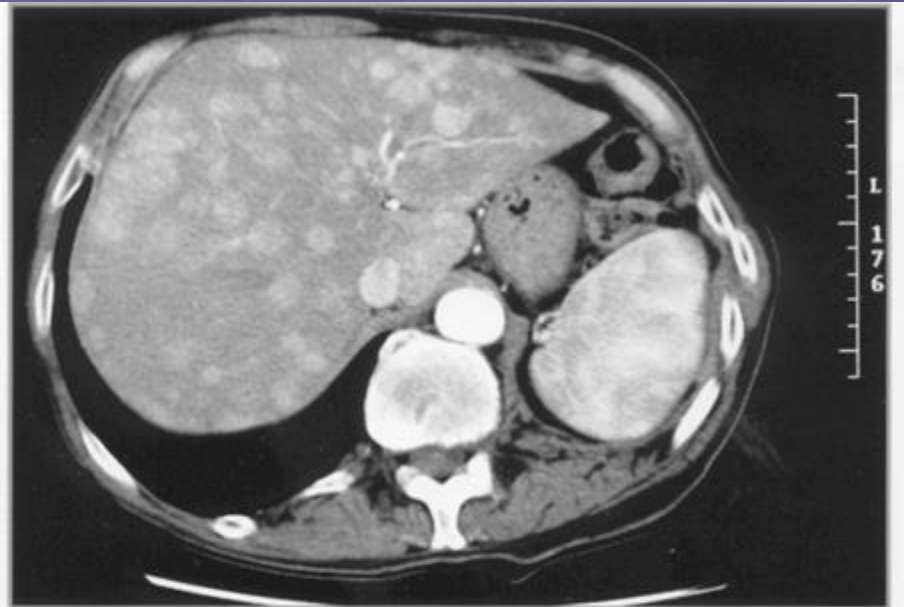
1. Astruc B et al. J Clin Pharmacol 2005; 45: 836-844

Endocrine Imaging



- Which imaging modality or combination ?

Arterial and venous phase CT



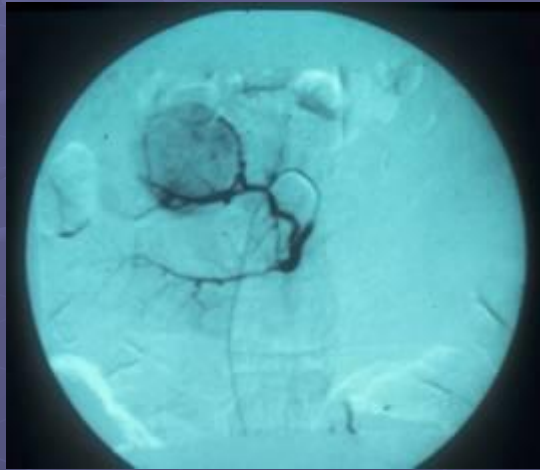
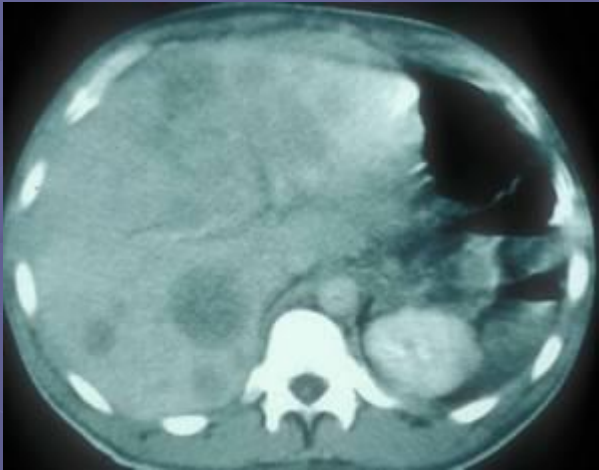
Spiral CT scan of abdomen. Arterial phase, showing metastases in liver (paler areas).



Spiral CT scan of abdomen. Venous phase, showing metastases in liver (dark areas).

Hypervascular metastases – amenable to arterial embolization

Interventional Radiology for Carcinoid



Particle embolization of hepatic metastases

Can greatly reduce symptoms and decrease
reliance/cost of biotherapy

See your way clear.

OctreoScan[®]

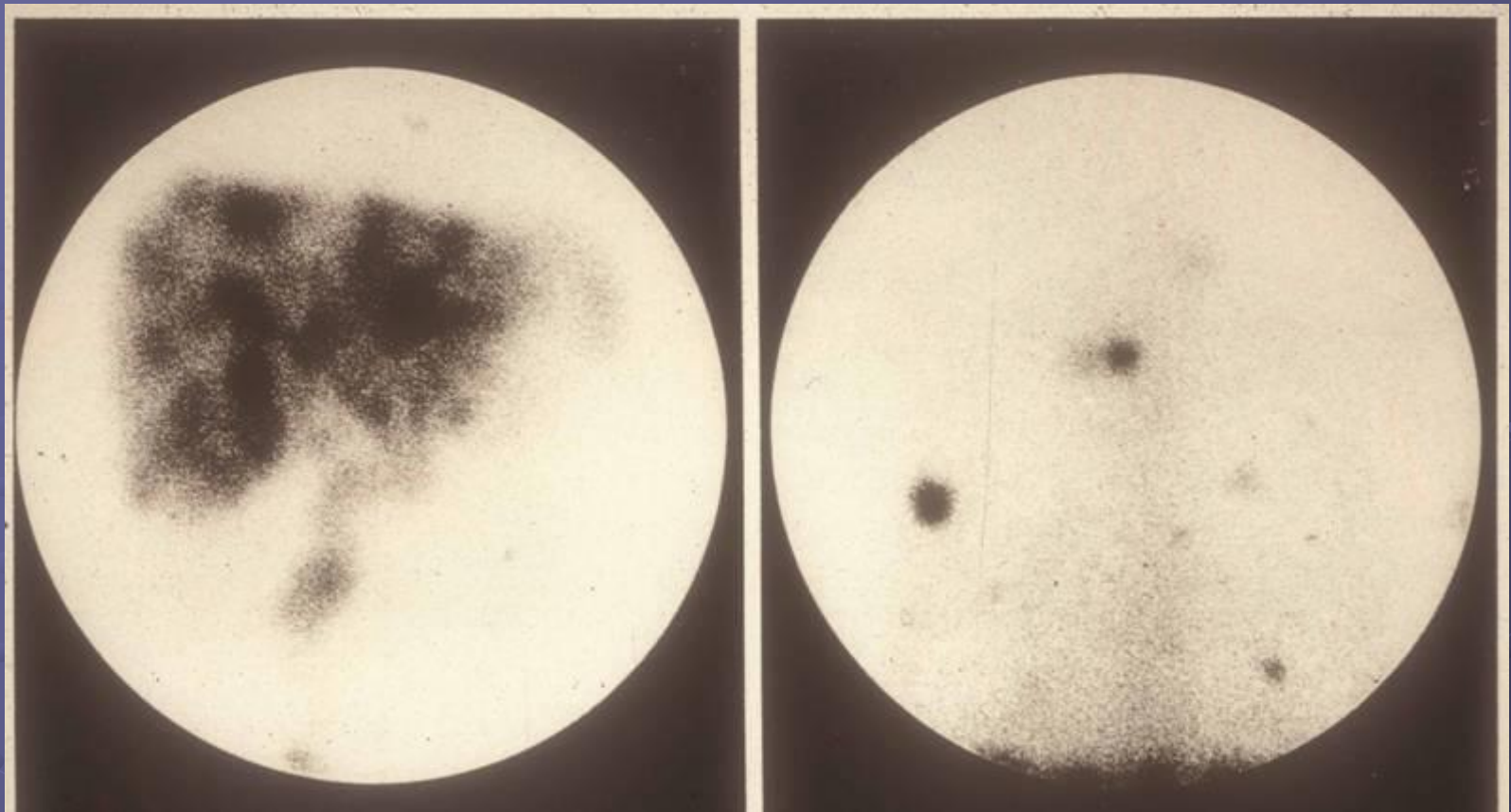
an In Vivo Diagnostic Radiopharmaceutical

uncovers

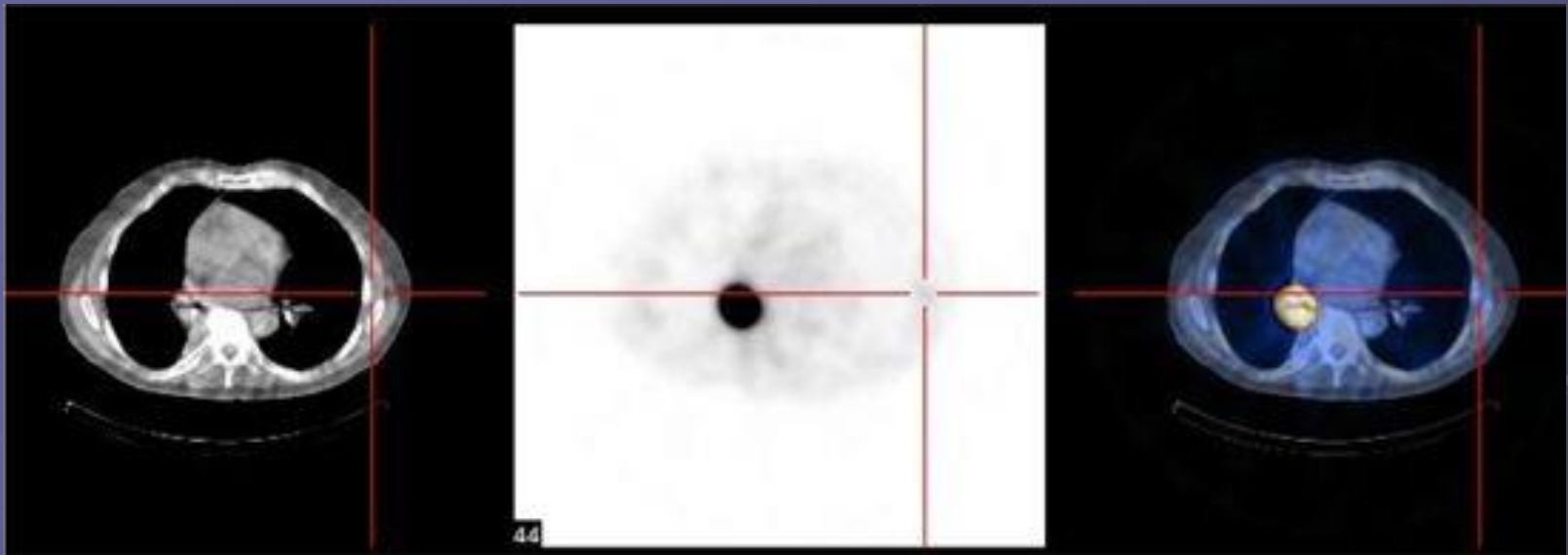
the undetected

MALLINCKRODT

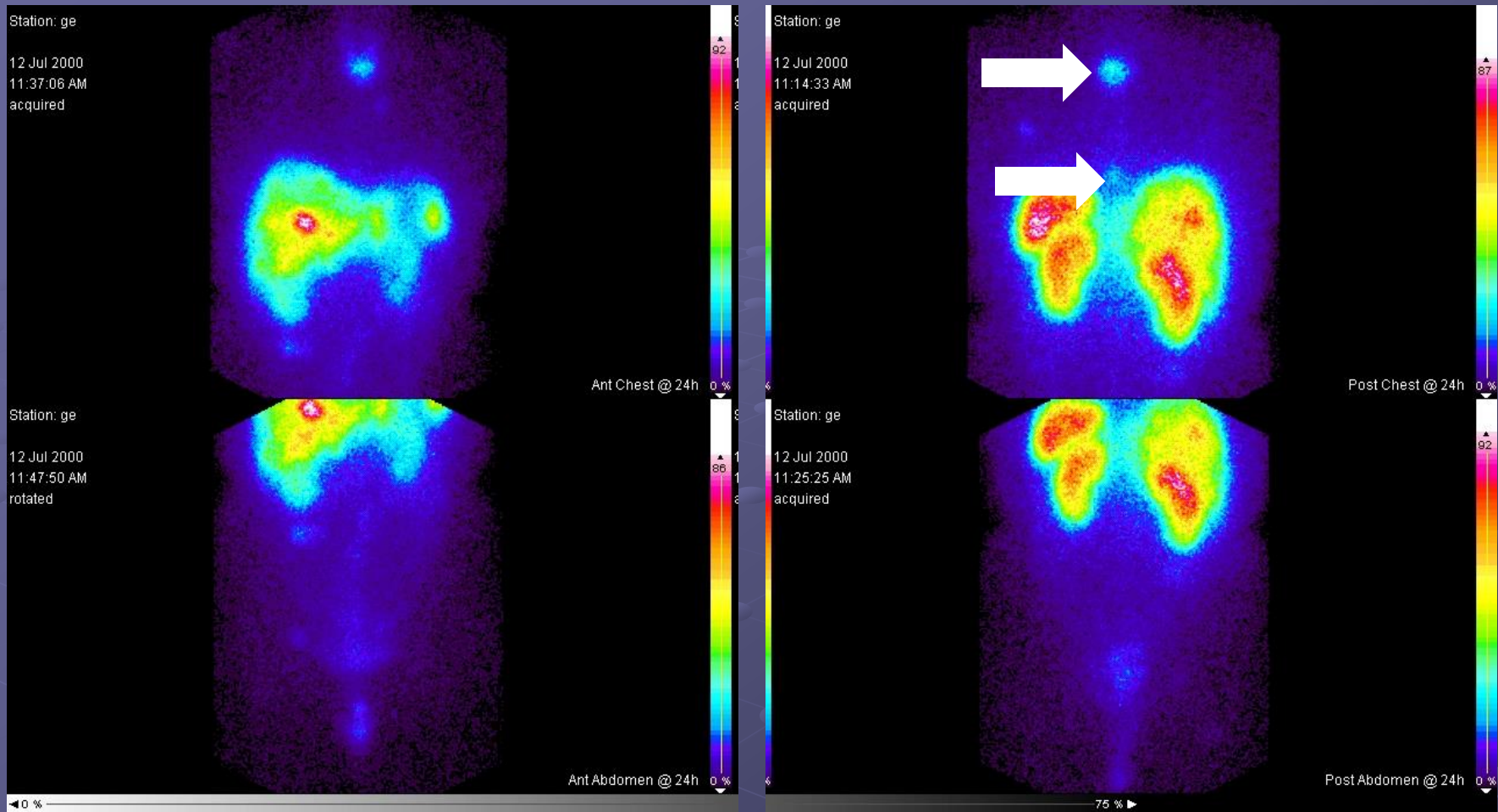
Clinical Cases where
Octreoscan has influenced
management



Octreoscan – for disease staging &
Predicting a response to SSA treatment



Computer generated fusion of CT and octreoscan
A fusion of FORM and FUNCTION



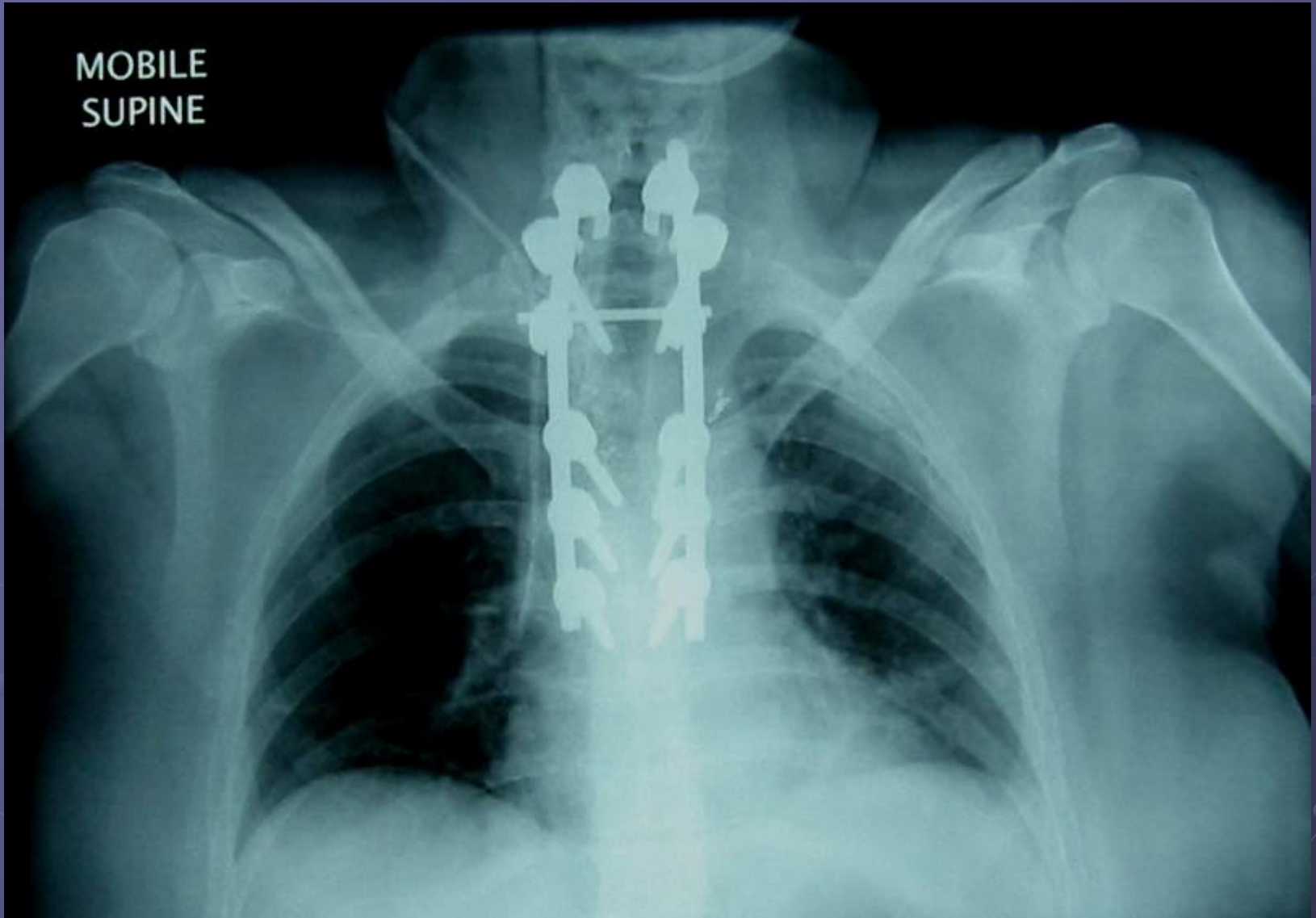
Metastatic carcinoid – the value of Octreoscan

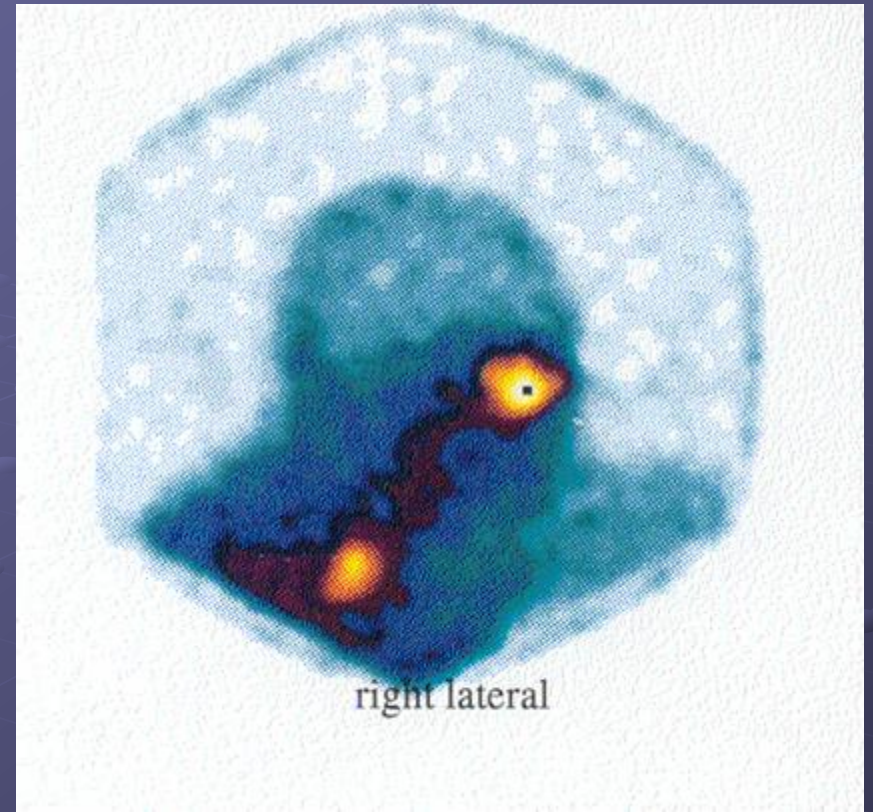
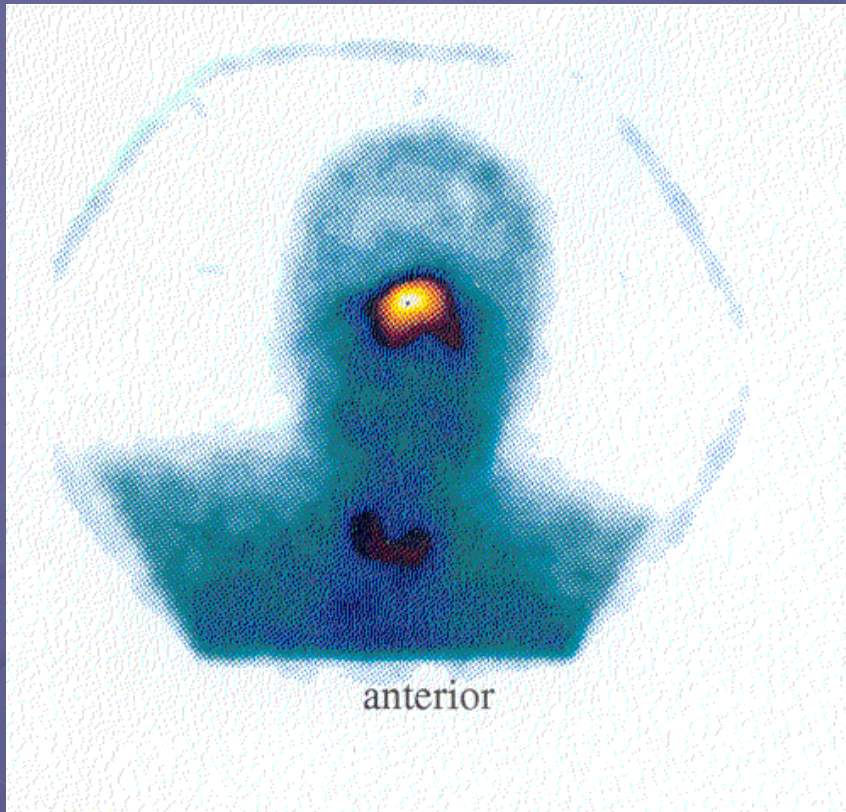


T2 Metastasis

- 1) Internal fixation
- 2) EBRT

MOBILE
SUPINE





Octreoscan – is SENSITIVE but not SPECIFIC



Need to know what you are looking at in the clinical context !

MW (dob 25/01/37) 63 yoa

- February 2000 RVI - PIU assessment
 - referred from Darlington January 2000:
 - complex partial seizures - CT scan 'tumour'
 - amenorrhoea (40 years!)
 - Single pregnancy at the age of 23
 - breast fed daughter 5 weeks (normal delivery)
 - 1 period post partum – nil since
 - Toxic goitre - Rx RAI \approx 1988 no Rx T4
 - appendectomy
 - hypertension: 30 years

MW

- O/E
 - hypothyroid
 - full visual fields
 - Mildly hypertensive
- cannulated prolactins: 310,590: 300,700
- MRI large prolactinoma extending to ethmoids and temporal lobe
- Normal STT
- 'Normal' TSH
- Low FT4

: 9

Mag 13.7x

POST CONTRAST

05 Jan 0
12:26:34 P
Mag = 1.
FL:
ROT:

4

-XL/90
600
11.5/EF
1/1 20.8kHz

D
:22x16.5
thk/0.2sp
03:58
X256/4 NEX



MW

● commenced

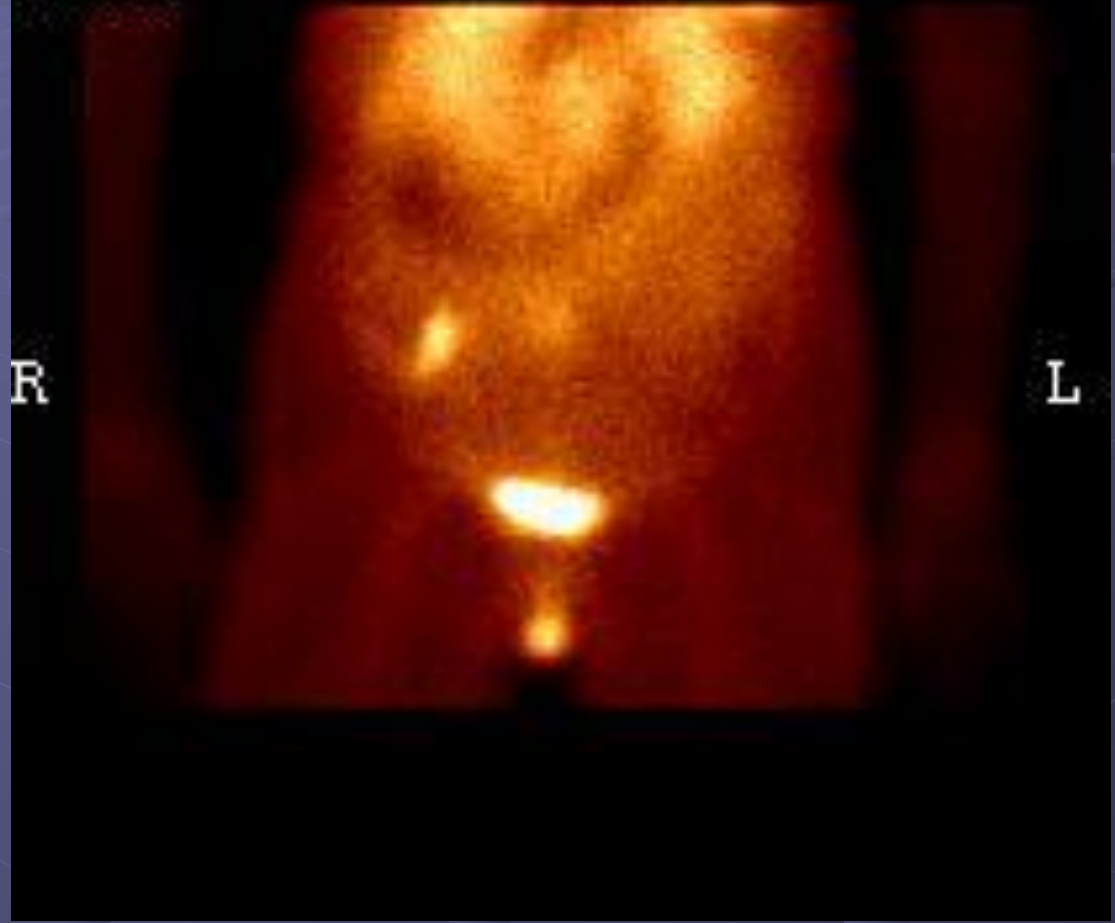
- Carbergoline 250 μ g twice weekly
- Thyroxine 50 μ g initially
- 'gratifying' response to Rx
 - Prolactin: 2,000 after 6 weeks (nr <450)
 - Lessening of temporal lobe symptoms
 - Modest shrinkage on repeat MRI at 6 months
 - Improved energy levels

MW – A new problem !

- Sept 2001: referred to local Gynaecologist
- weight loss, distended abdomen
 - U/S gross ascites
 - CA 125: 1,635 IU/l ? Ovarian CA
 - laproscoped:
 - 'breast milk' ascites
 - 'must be due to Prolactin' !!!!!
 - [Gynae diagnosis !]
 - 'nodules' ant abdo wall/ peritoneum - biopsied
- CT ? Liver mets
- The WORST WAS FEARED !
- HISTOLOGY: Carcinoid, Ki 67 2%

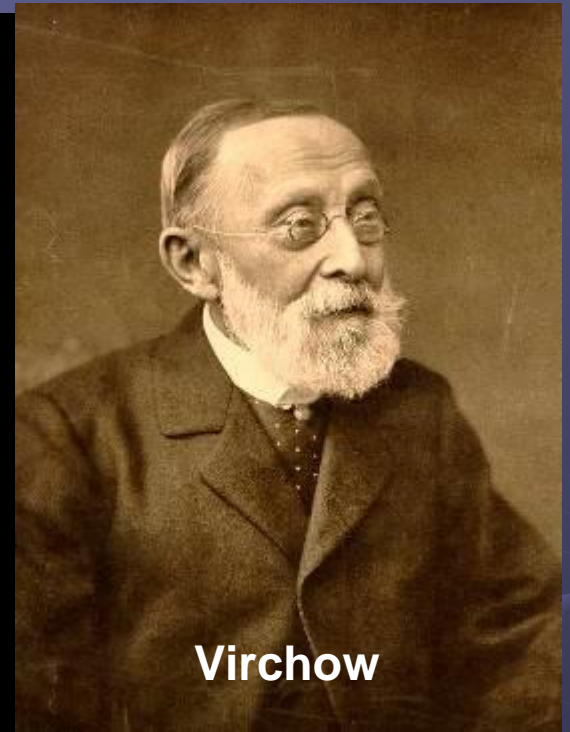
Anterior
600s
3939k

0:60

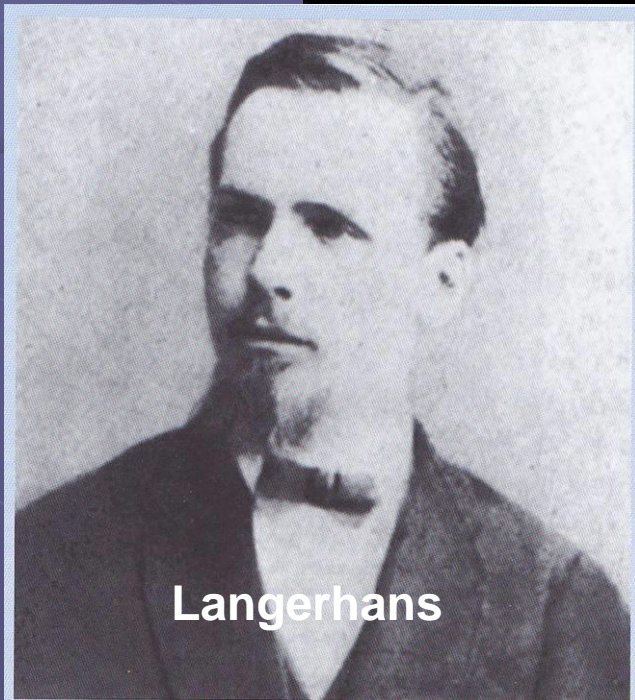


Octreoscan

Anterior
600s
1312k



Virchow



Langerhans



Octreoscan

Posterior
500s
1132k

Planar



Octreoscan

MW

- 5 HIAA: mildly elevated 127 (nr <40)
- fasting gut hormones elevated
 - CgA 159 (nr <30)
- minimal secretory symptoms
- *chylous ascities, secondary to thoracic duct involvement and blockage*

MW - Management

- Surgical drainage of chylous ascites
- Medical treatment:-
 - Sandostatin LAR – 20mg/month
 - Interferon 3MU/ x3 per week
 - Diet of medium chain triglycerides



MEMORANDUM FOR THE DIRECTOR
SUBJECT: [Illegible]

NEW
[Illegible]

REVISIONS
[Illegible]

DATE REVISION
[Illegible]

APPROVAL
[Illegible]

BY
[Illegible]

REASON
[Illegible]

REFERENCE
[Illegible]

APPROVED
[Illegible]

DATE
[Illegible]

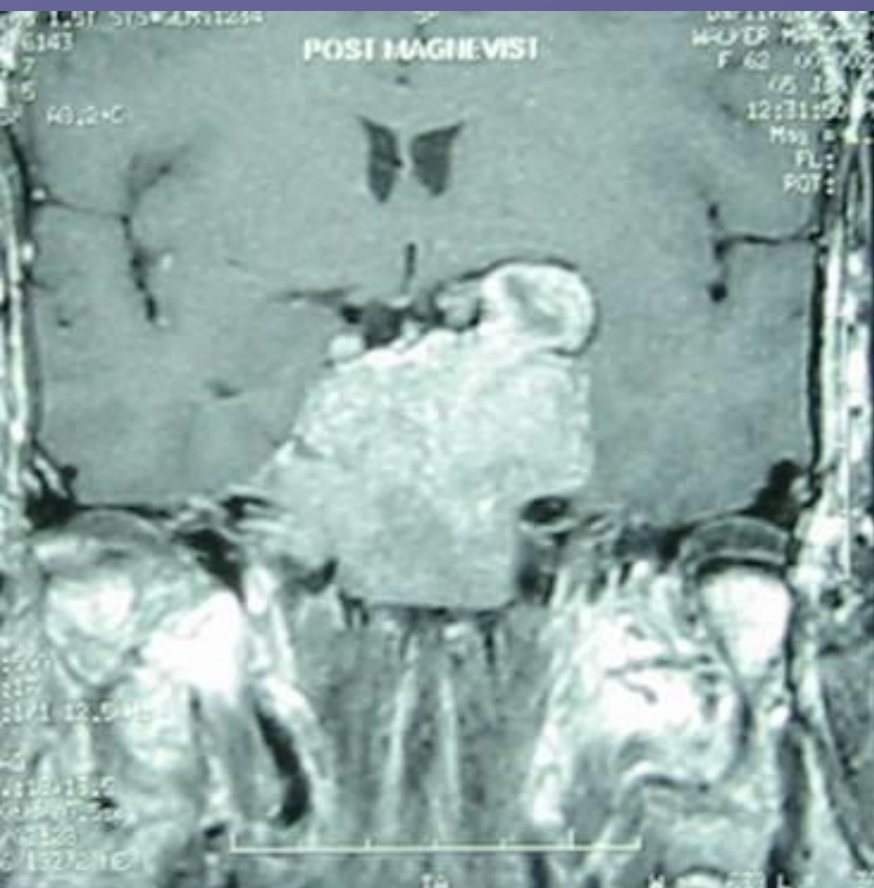


C
RE

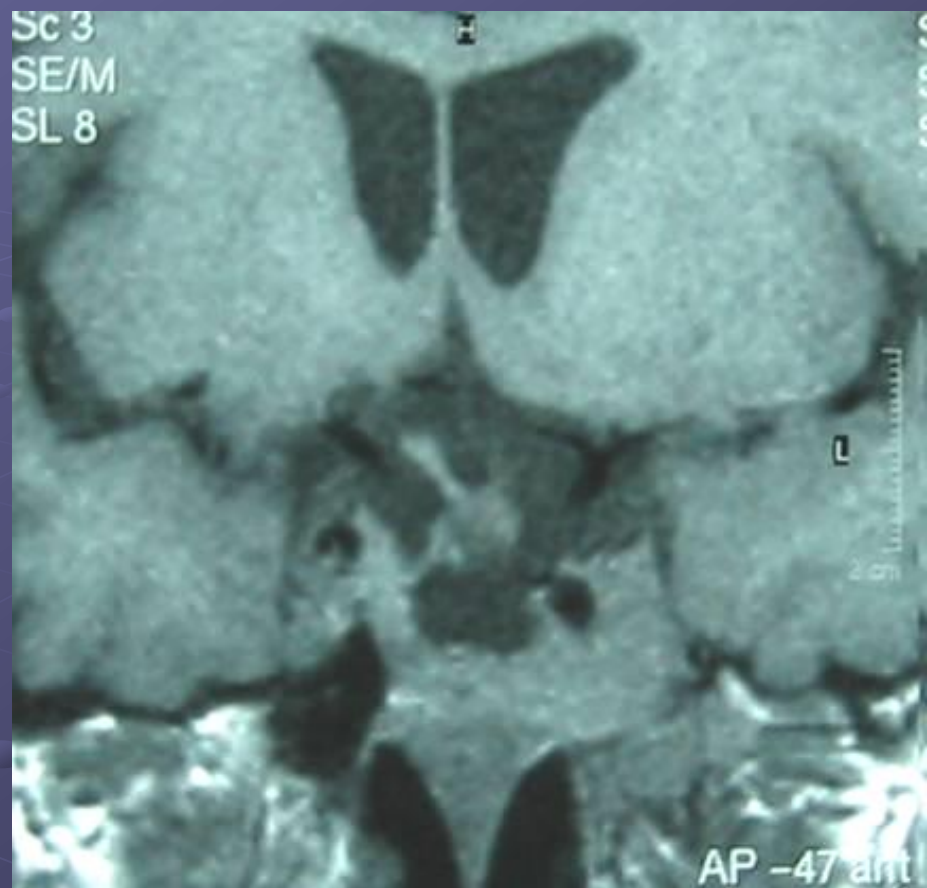
Chylous ascites

MW - Outcome

- Now completely well
 - Weight gain
 - Resolved ascites
 - Resolved Virchow's node
 - ? Recannulation of thoracic duct
- Also
 - Prolactin now 45 (nr <450)
- Additive effect of cabergoline and octreotide on prolactinoma – further involution of pituitary prolactinoma
- Benefits of combined interferon Rx



Pre-Rx



Post Cabergoline +
SSA



MW - Metastatic Carcinoid Diagnosed 2001 – picture 6/6/05 !

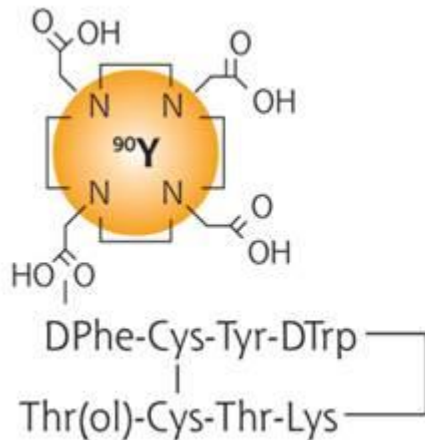
Still going strong May 2010

Octreotide scintigraphy (Octreoscan®)

- non-invasive whole-body examination
- staging of disease
- alters management in >40% of patients
- predictive test for treatment with somatostatin analogues
- Target for radioliganded analogues
- problem: small tumours and tumours lacking sst2 receptors

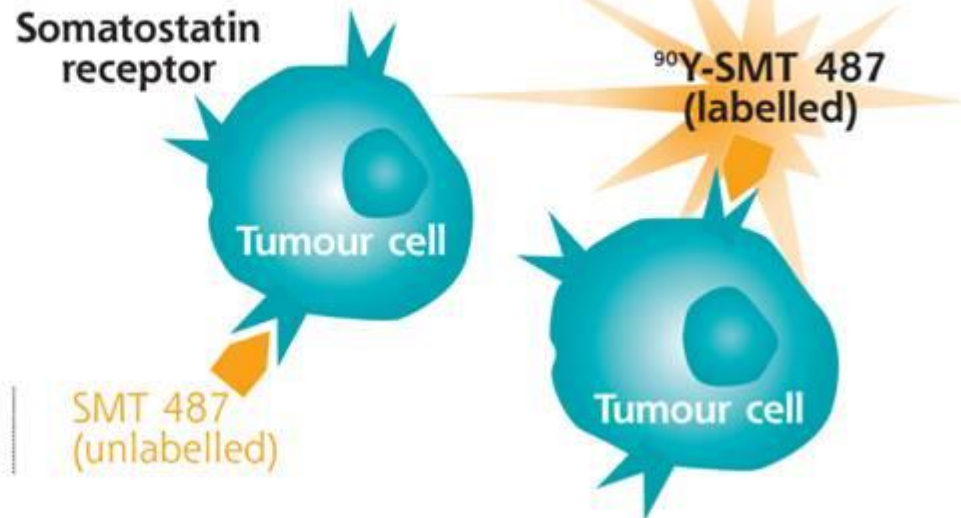
Radiolabelled somatostatin analogues: 90Y-SMT 487

STRUCTURE:



⁹⁰Y-DOTA-DPhe¹-
Tyr³-Octreotide

MECHANISM OF ACTION:



Yttrium-90 is a high energy beta emitter with a mean range of 5mm in tissue and a physical half-life of 64 hours. ⁹⁰Y has therapeutic (cytotoxic) potential

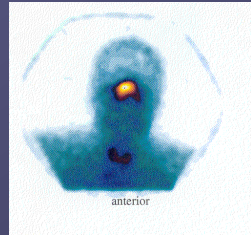
The β⁻-emitter labelled somatostatin analogue delivers a lethal radiation dose to the tumour cell



Somatostatin Analogues - The Future

● Design of subtype specific analogues

- Pan-receptor analogues (SOM-230)
- Chaemeric analogues (Dopastatin)



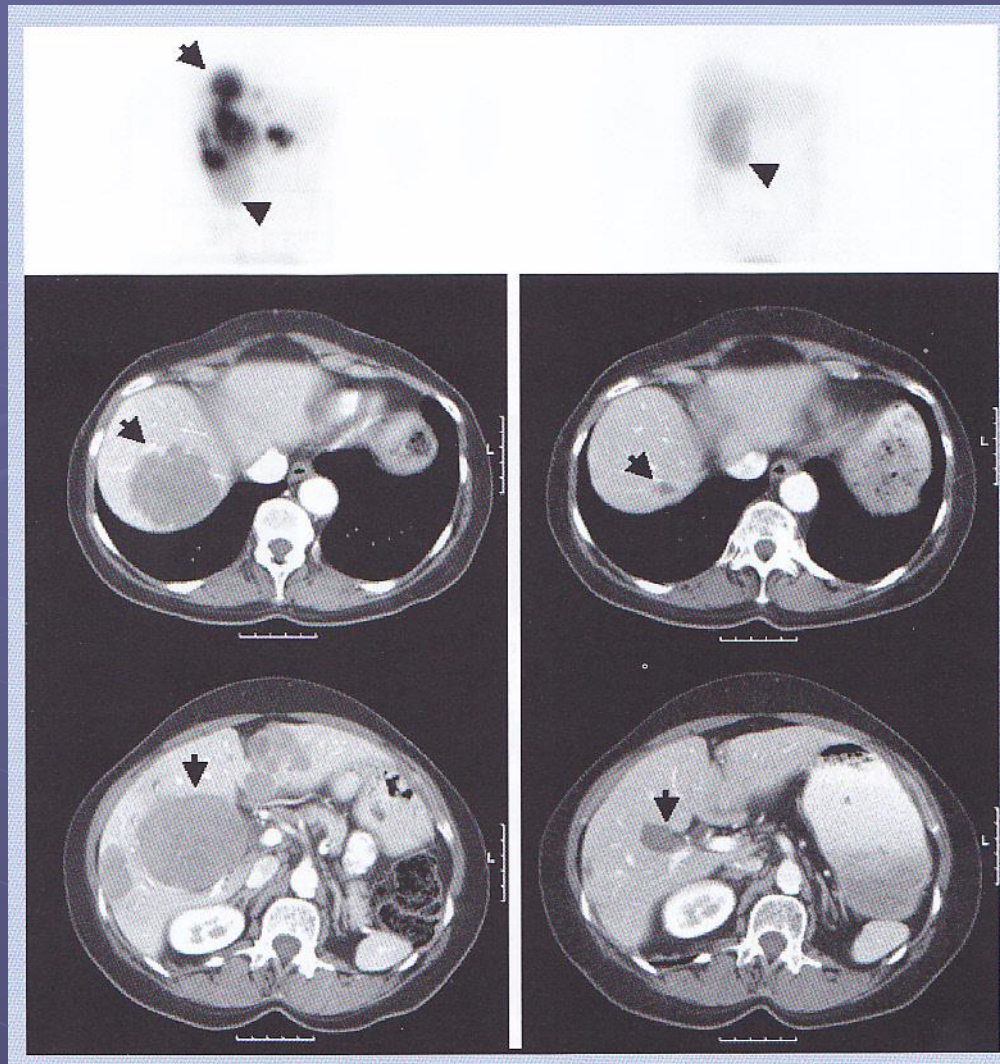
● More potent and specific radioligands

- Lutetium¹⁷⁷ – octreotate (beta and gamma)
- Yttrium⁹⁹ – octreotate (beta)

● Combination therapy

- Interferon
- Serine/Tyrosine Kinase inhibitors
 - evorolimus

● ‘Gene therapy’ to insert or overexpress sstR’s



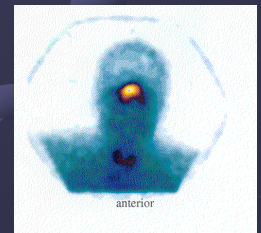
- **Metastatic NET Rx cycles of Lu¹⁷⁷ OCTREO-DOTATATE**
 - **Octreoscan (In ¹¹¹ before and after)**
 - **CT before and after**

Somatostatin Analogues - The Future

● Improved imaging

■ Ga-68 Octreotate

- Increased affinity for sst2 over Indium-111 pentetreotide (octreoscan)
- Better SSR subtype affinity (sstR 2,3,5)
- ? More predictive of response to treatment and radioligand ablation
- Also a PET ligand
- Better diagnostic and staging potential



Gallium 68-Octreotate PET

FDG 18 PET

Before and after treatment with
Yttrium ⁹⁰ – labelled Octreotate

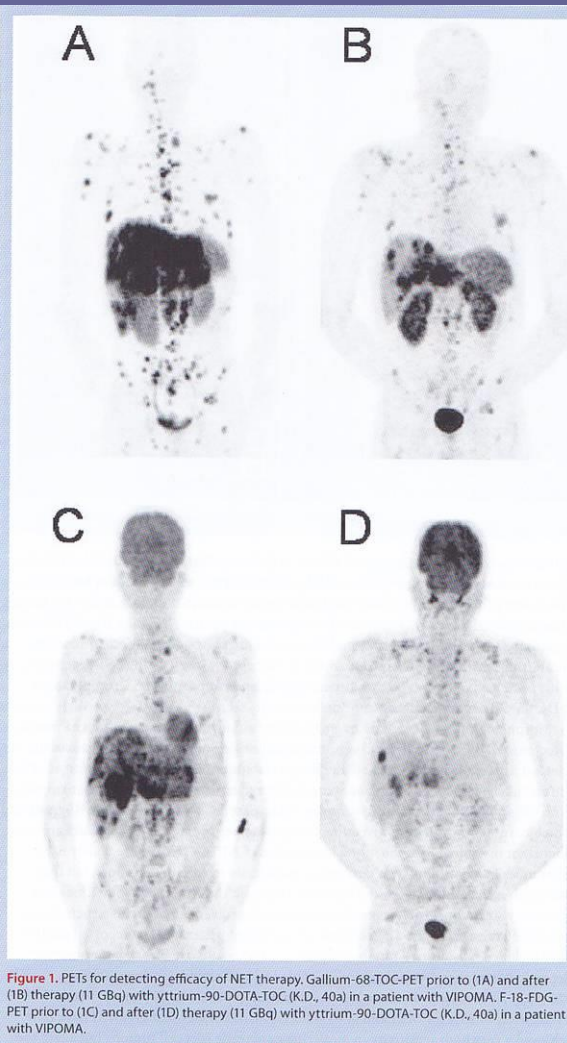
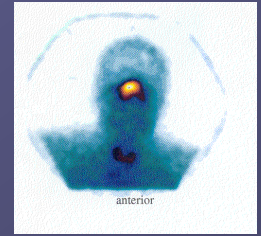


Figure 1. PETs for detecting efficacy of NET therapy. Gallium-68-TOC-PET prior to (1A) and after (1B) therapy (11 GBq) with yttrium-90-DOTA-TOC (K.D., 40a) in a patient with VIPOMA. F-18-FDG-PET prior to (1C) and after (1D) therapy (11 GBq) with yttrium-90-DOTA-TOC (K.D., 40a) in a patient with VIPOMA.

Conclusions - NET tumours



- Multidisciplinary/multimodal approach
 - UKINET/ENETS - guidelines and trials
- Somatostatin analogues can relieve symptoms, reduce circulating hormone levels and stabilise tumour growth in >50% of patients with neuroendocrine tumours
 - Antiproliferative effect modest
 - Subtype - specific or pan-somatostatin analogues may improve the results
- Can be used as single agents or in combination with other therapeutic modalities
 - Interferon
 - Tyrosine kinase inhibitors (PROMID study)
- Expect vast improvement in PET ligands for imaging
- Treatment with radiolabelled somatostatin analogues holds great promise for the future



Thank You – on behalf of the Newcastle NET service